Biotechnology Innovation Organization

February 5, 2017

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted Electronically via Federal eRulemaking Portal (http://www.regulations.gov)

Re: Docket No. FDA-2017-N-5093. Review of Existing General Regulatory and Information Collection Requirements of the Food and Drug Administration.

Dear Sir or Madam:

The Food and Agriculture Section of the Biotechnology Innovation Organization (BIO) is pleased to submit these comments in response to the U.S. Food and Drug Administration's (FDA) request for public input on a notice published in the *Federal Register*[1] entitled "Review of Existing General Regulatory and Information Collection Requirements of the Food and Drug Administration," as well as several related Center-specific notices. Because the issues raised in our comments often relate to more than one FDA Center, we provide here one consolidated set of comments, indicating to which Center or Centers the comments refer, and submit a copy of these comments to the respective dockets for the the individual centers referenced herein. In particular, our comments relate to the Center for Biologics Evaluation and Research (CBER),[2] Center for Drug Evaluation and Research (CDER),[3] Center for Devices and Radiological Health (CDRH),[4] the Center for Food Safety and Applied Nutrition (CFSAN),[5] and the Center for Veterinary Medicine (CVM).[6]

BIO is the world's largest trade association representing roughly 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products. BIO represents many of the agricultural biotechnology product developers in North America, including companies developing products affected by actions of one or more FDA Center.

FOODS DERIVED FROM NEW PLANT VARIETIES (CFSAN, CVM)

In 1986, the U.S. White House Office of Science and Technology Policy articulated general policies and principles for the oversight of certain products of agricultural biotechnology in a document entitled the "Coordinated Framework for the Regulation of Biotechnology" (the Coordinated Framework).[7] FDA's

[1] 82 FR 42506-42507 (September 8, 2017).
[2] Docket No. FDA-2017-N-5092. 82 FR 42492-42494 (September 8, 2017).
[3] Docket No. FDA-2017-N-5101. 82 FR 42499-42501 (September 8, 2017).
[4] Docket No. FDA-2017-N-5105. 82 FR 42494-42497 (September 8, 2017).
[5] Docket No. FDA-2017-N-5094. 82 FR 42503-42506 (September 8, 2017).
[6] Docket No. FDA-2017-N-5104. 82 FR 42947-42499 (September 8, 2017).
[7] OSTP. 1986. Coordinated Framework for Regulation of Biotechnology. 51 Fed. Reg. 23302, 23304

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role within the Coordinated Framework was described in a 1992 policy statement, *Foods Derived from New Plant Varieties*,[8] implementing the principles of the Coordinated Framework with respect to food and feed safety of plants and plant products. FDA's 1992 policy offers an explanation of the rationale it uses to formulate a science-based approach to safety reviews, and forms the basis of a voluntary process by which developers may consult with FDA regarding the safety of foods derived from new plant varieties before bringing such foods to market.[9] This consultation process is jointly administered by CFSAN and CVM.

While we agree that the consultation process has worked well for nearly 30 years, we strongly encourage FDA to identify mechanisms by which it can better incorporate its experience over time and, where possible, implement more efficient, streamlined review processes for those products similar to those the agency has reviewed in the past. United States Department of Agriculture (USDA) regulations, for example, include a streamlined "extension" process[10] for more efficient reviews of products of agricultural biotechnology sufficiently similar to those previously reviewed by the agency. FDA should consider implementation of similar mechanisms to parallel USDA's review process.

An additional, significant shortcoming of the premarket consultation process at FDA is that reviews independently conducted by CFSAN and CVM are partially, if not wholly, redundant with each other. This creates significant inefficiencies for the Agency, as well as creating the possibility that reviews for similar food safety risks are implemented inconsistently across the two centers. We encourage FDA to develop a less redundant review process (such as reciprocity if no material differences are identified) that better coordinates expertise across CFSAN and CVM into a single, efficient review.

REVIEW OF GENETICALLY ENGINEERED ANIMALS CONTAINING HERITABLE RECOMBINANT DNA CONSTRUCTS (CVM, CDRH, CDER, CBER)

Background

BIO members include companies that use recombinant DNA technology to create genetically engineered (GE), or transgenic, animals that lead to a very diverse array of end products:

1. Transgenic animals, which are then used in basic and applied research to a) understand basic biological functions in health and disease, and b) use for testing during the development of pharmaceutical products.
2. Transgenic animals that are used to produce pharmaceutical end products, including therapeutic molecules, cells, tissues and organs.
3. Transgenic animals that are companion animals or pets.
4. Transgenic animals, or their products, that are intended for the food supply.
5. Transgenic insects that are intended to prevent spread of insect-vectored diseases.

[8] FDA. 1992. Statement of Policy: Foods Derived from New Plant Varieties. 57 FR 22984-23005.
[9] FDA. 1997. *Consultation Procedures under FDA's 1992 Statement of Policy - Foods Derived from New Plant Varieties*. https://www.fda.gov/RegulatoryInformation/Guidances/ucm096126.htm
[10] 7 CFR 340.6(e)

CVM regulates the heritable DNA construct as a new animal drug, based on the definition of a drug in section 201(g) of the Federal Food, Drug and Cosmetic Act (FDCA), specifically "articles (other than food) intended to affect the structure or any function of the body of the man or other animals." Therefore, certain transgenic animals currently being developed are subject to oversight by two FDA Centers. For example, in category 2 described above, a human therapeutic end product produced by a transgenic animal must be approved by a human-health center, such as the Center for Drug Evaluation Research or the Center for Devices and Radiological Health, while the genetic construct is approved as a new animal drug.

All heritable DNA constructs inserted into animals using rDNA technology meet the definition of a drug and, therefore, according to the FFDCA are "deemed unsafe" unless FDA has approved a new animal drug application (NADA) or the drug is only for investigational use and qualifies for an Investigational New Animal Drug (INAD) exemption.[11] However, CVM has opted to exercise enforcement discretion with regard to its NADA and INAD requirements for certain GE animals, based on the risk(s) they pose. For example, CVM has not enforced its NADA and INAD requirements for GE animals of non-food-species that are raised and used in contained and controlled conditions such as GE laboratory animals used in research institutions. CVM has also exercised a form of enforcement discretion over its INAD and NADA requirements for additional kinds or uses of non-food-species GE animals, such as *Zebra danio* aquarium fish genetically engineered to fluoresce (GloFish®).

However, the conditions and obligations for maintaining enforcement discretion differ for these two categories of GE animals. Developers of laboratory rodents used in research labs are not required to contact FDA or provide data packages for each new line of GE rodents in order to maintain enforcement discretion for a category of GE animals. They are free to commercialize each new line of GE rodent as soon as it is produced. For other non-food GE animals that have received enforcement discretion, FDA continues to use case-by-case review. In those cases, developers are required to make a separate enforcement discretion request for each line of GE animal they plan to commercialize, because FDA considers each insertion of a genetic construct, including previously approved constructs inserted into the same species, as a separate new animal drug that is subject to INAD and NADA requirements. Each request must be supported by a lineage-specific, detailed data package, and marketing cannot begin until (and unless) FDA grants lineage-specific enforcement discretion status.

Experience with GE Animals Regulated as New Animal Drugs

In developing its draft 2009 Guidance for Industry document 187, *Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs*, FDA assumed that a mandatory premarket review and approval of GE animals would 1) promote public confidence in their safety, and 2) establish a clear path to market that would encourage innovation that would improve

[11] 21 USC 360b (a)(1), (a)(3)). An exemption also applies if the drug is used in conformance with regulations promulgated under sections 512(a)(4) or (5) of the Act (21 U.S.C. 360b(a)(4) or (5)).

human health, animal health and food safety. Industry agreed with FDA's approach and goals.[12] However, since 2009, FDA has approved only:

- three human therapeutics produced by GE animals, with CDER approving the drug and CVM approving the transgenic construct; and
- one GE animal intended for the food supply, the AquAdvantage salmon.

Recently, regulatory review of GE animals was moved from a cross-disciplinary group of animal biotechnology experts, which was housed in the CVM Director's Office, to the Office of New Animal Drug Evaluation (ONADE). This move appears to have encouraged an expansion of both pre-market data requirements and post-market oversight requirements. While such requirements might be appropriate in the case of traditional drugs administered to animals, they are unrelated to any specific risks posed by the GE animals.

For example, it is our understanding that establishment registration and drug listing are now required for all commercialized products (including those that receive enforcement discretion). While this may be a very valid requirement for drug manufacturing as it relates to facilitating inspections, it is unclear how this would work in potential cases such as livestock producers and fish markets that may one day sell live GE animals.

In addition, it appears that academic and government researchers conducting basic research using covered GE animals are now expected to contact FDA before creating a GE animal, even though the researcher has no interest in commercializing the GE animal as a product. This will severely impede basic research that provides fundamental information on biological function in health and disease. To reduce the severe barriers to innovation that have been created by FDA's interpretation of genetic constructs as drugs, BIO encourages FDA to consider creating additional broad categories of enforcement discretion, similar to those created for laboratory rodents, for other GE animals, based on the risk(s) they pose.

GENE EDITED ANIMALS (CVM)

On January 19, 2017, CVM announced a proposed expansion of the scope of draft GFI 187 to include animals with genetic material that had been intentionally altered, as any intentional genetic modification meets the statutory definition of a drug.[13] However, in the draft guidance CVM acknowledged that long–established animal breeding practices and mutagenesis induced by chemicals or radiation also lead to genetic modification and, therefore, meet the statutory definition of a drug. However, CVM chose to exclude such methods from oversight. Therefore, CVM limits its oversight to animals whose genomes have been intentionally altered using "modern molecular technologies," thus

[12] Lutter, Randall and Lena Lewis. 2107. How to Regulate Genome Edited Animals? A Comment on FDA's Proposed Guidance Docket ID No. FDA-2008-D-0394 at https://scholarspace.library.gwu.edu/downloads/g158bh310

[13] 82 Fed. Reg. 6561 (Jan. 19, 2017) and FDA-CVM. January 2017. Draft Guidance. *Regulation of Intentionally Altered Genomic DNA in Animals*. https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf

excluding animals produced with the least precise mechanisms of genetic modification, breeding and random mutagenesis, from oversight.

The majority of those who submitted comments on the proposed revisions to draft GFI 187, including BIO, urged FDA to reconsider this expansion of scope because:

- The proposed revisions are not based on science or risk.
- The scope of oversight explicitly focuses on the genetic modification process and not the product. Therefore, it departs from the US government's longstanding position on appropriate regulation of biotechnology products.
- The expanded scope will significantly impede development of innovative products with substantial benefits to animal welfare, consumers, the environment and animal producers with no compensatory benefit of protection of health or the environment to offset the significant costs.

If CVM subjects basic research on gene edited animals, carried out by public sector scientists, to the requirement of contacting FDA prior to initiating research (see above), the negative impacts on basic research on gene function in health and disease will be stunning.

In the submitted comments,[14] BIO and others urged CVM to withdraw the proposed revisions to GFI 187. We repeat that same request here.

In addition, BIO supports the position that, where it can be shown that a new trait has been provided to animals using genome editing tools that are essentially a more precise method of animal breeding, the resulting animals should not be treated differently for purposes of pre-market review than those animals modified through more traditional breeding methods that have a history of safe use and for which CVM has decided do not need premarket oversight.

Finally, as stated above, even though all intentional genetic alterations meet the definition of a drug, BIO encourages FDA to follow the precedent it created for GE animals by establishing broad categories of enforcement discretion, similar to those created for GE laboratory rodents, for genome-edited animals, based on the risk(s) they pose.

VOLUNTARY LABELING OF FOODS DERIVED FROM GENETICALLY ENGINEERED PLANTS (CFSAN)

FDA has authority under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that information provided on certain food products is not false or misleading. In 2015, FDA issued updated guidance for industry regarding voluntary labeling of products with information about whether the product had been derived (or not) from genetically engineered plants.[15] Many products on the market today make

[14] https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=PS&D=FDA-2008-D-0394

[15] FDA. 2014. *Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Derived from Genetically Engineered Plants.* https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm059098.htm

such voluntary claims about the presence or absence of ingredients derived from such plants. We encourage FDA to review whether these products are currently being labeled consistent with the FFDCA and FDA guidance, and to use its enforcement authorities to ensure that such claims are truthful and not misleading.

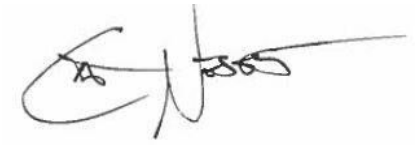
FOOD ADDITIVE REVIEW (CFSAN, CVM)

FDA has premarket review authority under the FFDCA over food additives. A food manufacturer can add a substance to human or animal food without FDA's premarket review or approval if the substance is generally recognized as safe, among qualified experts, under the conditions of its intended use (GRAS). In 2016, FDA finalized new rules clarifying when a substance is eligible for classification as GRAS and streamlining its evaluation of manufacturer conclusions of GRAS status. The final rule replaced the procedure for petitioning to affirm GRAS status with a voluntary procedure for notification of a conclusion of GRAS status.

BIO applauds FDA for recognizing and taking steps to improve the evaluation and approval of GRAS status. However, the Agency can still make significant improvements in the animal food additive space, as there remains significant confusion and difficulty in determining what additives qualify as GRAS. One way to alleviate some of the difficulties would be for CVM to affirm the GRAS status of the all the ingredients listed in the Official Publication of the Association for American Feed Control Officials (AAFCO). This should not be a heavy lift as CVM has already reviewed the safety of these ingredients. Additionally, BIO recommends that FDA set up a Select Committee on GRAS Substances (SCOGS) to evaluate any materials of possible concern on the AAFCO list. Finally, many additives are used in both human and animal food. CVM and CFSAN should prioritize developing uniform policies and procedures for the review and affirmation of GRAS status. One set of procedures would greatly reduce the burden on manufacturers seeking GRAS status for additives used both in animal and human food. Also, further streamlining the GRAS process would free up limited resources in CVM and CFSAN to more quickly investigate and remove unsafe food ingredients and food additives from the supply chain.

Thank you for the opportunity to provide comments on the dockets related to FDA's review of existing regulatory and information collection requirements. Please feel free to contact me directly if you have any questions about our comments.

Sincerely,



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